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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/720,006	KARL ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-48,73,75-77,81 and 82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-48,73,75-77,81 and 82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/6/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/6/2009 has been entered.

2. Claims 44 and 47 were amended. Claims 78-80 were canceled. Accordingly, claims 44-48, 73, 75-77, and 81-82 are currently pending and subject to examination below.

Terminal Disclaimer

3. The terminal disclaimer filed on 11/14/2008 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. 6,815,217 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Objections/ Rejections Withdrawn

4. The rejections of claims 78-80 are moot in light of Applicant's cancellation of these claims.

5. The rejections under § 112, 2nd paragraph as set forth in the previous Office action have been withdrawn in response to Applicant's amendments.

6. The rejections of claims 44-45, 47-48, 73, 76-77, and 81 under § 102(a) as being anticipated by Karl et al. (WO 99/05525) have been withdrawn in response to Applicant's

amendments to claim 44 to recite that the test area-specific background is detected by signal-generating group non-specifically bound to the first or second test area.

7. The rejections of claims 44-45, 47-48, 73, and 75-77, and 81 under § 103(a) as being unpatentable over O'Connor, of claim 46 as being unpatentable over O'Connor in view of Ekins, and of claim 82 as being unpatentable over O'Connor in view of Miyamura et al. have also been withdrawn in response to the above-mentioned amendments to claim 44.

8. The rejections of claims 44-48, 73, and 75-80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 6,815,217 have been withdrawn in view of the above-mentioned terminal disclaimer.

Priority

9. Acknowledgment is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/EP99/04310, filed 6/22/1999. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Application No. 198 27 714.8, filed on 6/22/1998, and to Application No. 198 38 802.0, filed 8/26/1998, both in Germany.

10. Applicant's filing of certified translations of the two foreign priority applications on 7/6/2009 is acknowledged. Upon review of the translations, the instant claims are not entitled to the earlier priority dates for the following reasons.

Step (d) of independent claim 44, as amended instantly, recites:

> calculating a test area-specific cutoff on each test area based on a test area-specific background measured in the absence of the plurality of analytes, wherein the test area-specific background is detected from a signal generated by any signal

> generating group non-specifically bound to the at least first or second test area in the absence of any analyte of the plurality of analytes,
>
> wherein the signal generated in the presence of the plurality of analytes by the signal generating group bound to the first or second test area above the test area-specific cutoff is classified as a positive result, and wherein a positive result obtained from at least one of the first and second test areas is indicative of the presence of the pathogen in the sample.

Under 35 U.S.C. 119 (a) or (e), the claims in a U.S. application are entitled to the benefit of a foreign priority date or the filing date of a provisional application if the corresponding foreign application or provisional application supports the claims in the manner required by 35 U.S.C. 112, first paragraph. See MPEP 2163.03 and 201.15.

In the instant case, Applicant has argued for patentability over the prior art of record on the basis of the indicated subject matter (see the instant Reply, page 10) and indicates support in the instant specification on page 10, third paragraph; page 11, first paragraph; page 21, second paragraph step (c); page 21, last paragraph to page 22, fourth paragraph; in Examples 2-5, and in original claim 42 (see Reply, page 5).

However, no corresponding disclosure could be found in the foreign priority applications. In particular, no mention could be found of a "test area-specific background measured in the absence of the plurality of analytes" or of cutoffs calculated on the basis of *test area-specific backgrounds*.

German Application No. 198 38 802.0 discloses cutoff limits that are specific for each test area (see especially pages 20-21). However, it is not disclosed that such cutoff limits are based on background measurements that are also test area-specific. In particular, Application No. 198 38 802.0 discusses measurement of a "sample-specific" background on page 10, but does not

disclose a "test area-specific" background. This disclosure of a "sample-specific background" therefore conveys a background that is specific to the *sample* to be measured, rather than to a particular *test area* as now claimed.

Application No. 198 38 802.0 also discloses the following equation on page 20:

$COI = signal_{sample} - background_{sample} / n \times background_{negative\ control.}$

However, there is suggestion that either the background of the sample or the background of the negative control are "test area-specific" or that they are measured in the absence of the plurality of analytes. Furthermore, it is not disclosed that the test area-specific background is detected from signal-generating group that is *non-specifically bound to the first or second test area*. Rather, Application No. 198 38 802.0 describes the use of control areas that do not contain any analyte-specific receptor (see claim 7). Such control areas cannot correspond to the currently recited "first or second test areas" as the latter have analyte-specific receptors bound thereto (see part (a) of claim 44).

Regarding German Application No. 198 27 714.8, although "sample-specific background" used to define a "sample-specific cutoff" is disclosed (page 10), no disclosure pertaining to test area-specific cutoff values or test area-specific background could be found. An equation for calculation of a cutoff index is disclosed on page 21, which includes the variable "$signal_{background}$". However, there is no suggestion that the sample-specific cutoffs would also be test area-specific.

In addition, as above there is no mention that the background is "test area-specific" or that it is measured in the absence of the plurality of analytes *non-specifically bound to the first or*

second test area. Rather, control areas that do not contain any analyte specific receptor are described (see claim 7). As such, neither explicit nor implicit support could be found for a test area-specific cutoff, or in particular for a test area-specific cutoff that is based on a test-area-specific background as recited instantly.

Furthermore, the instant claims also recite that the presence of the pathogen is indicated by a positive result obtained from *at least one of the test areas*. Application No. 198 27 714.8 discloses a different manner of interpreting the test results, in that *two or more test areas* must be positive (see page 6, lines 3-5).

For these reasons, the instant claims are not entitled to the benefit of the earlier filing dates because descriptive support for the currently claimed subject matter is not apparent in the prior applications. See also the rejection that follows under § 112, 1st paragraph for further analysis. Accordingly, the priority date has been set to 6/22/1999.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 44-48, 73, 75-77 and 81-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Step (d) of independent claim 44 has been instantly amended as quoted above.

Applicant states that no new matter has been added and indicates support in the specification on pages 10-11, 21-22, in Examples 2-5, and in original claim 42 (Reply of 7/6/2009, page 5). The Examiner was unable to find support where indicated.

On page 11, the specification discloses measuring a "sample-specific background" in order to define a "sample-specific cut-off". This cut-off value is a threshold value to differentiate between positive and negative values. The concept of **test area-specific cut-off values** is also introduced (page 11, second paragraph; pages 21-22; and original claim 42 ("the cut-off values are each determined individually for a test area")).

However, the instant claim now requires not only that the cut-off values themselves are test area-specific, but also that they are based on a **test area-specific <u>background</u>** that is measured in a particular manner, namely as any signal generating group non-specifically bound to the first or second test area in the absence of analyte.

Support could not be found for calculating cut-off values based on background measurements that are specific to each test area. Furthermore, support could not be found for performing background measurements by measuring signal generating group non-specifically bound to the first or second test areas in the absence of analyte.

The specification also discloses a "conventional calculation of the cut-off value (COI)" which includes the parameters background of the sample and background of a negative control (page 22):

$$COI=signal_{sample}-background_{sample}/nxbackground_{negative\ control}$$

Similar equations are also disclosed on page 30. However, there is nothing in the specification to convey that either of the two background parameters in this equation is intended to be "test area-specific". The disclosure of "background of the sample" suggests at best that the background is specific to the *sample*, and does not clearly convey that the background is also specific to each *test area*. Furthermore, there is nothing in the disclosure of the parameter $background_{sample}$ that conveys the particular manner of measurement now claimed, i.e. "detected from a signal generated by any signal-generating group non-specifically bound to the at least first or second test areas in the absence of any analyte".

Indeed, Applicant has previously argued on the record that the parameter $background_{sample}$ refers to "sample specific background measured for example from the inert solid phase between spots without a specific coating" (Reply of 11/14/2008 at page 12, second paragraph; the paragraph bridging pages 15-16; and page 19, third paragraph). Similarly, Applicant has argued that test area-specific background would be measured according to the instant invention as non-specific binding *to the inert solid phase*, rather than to the test areas themselves (Reply of 11/14/2008, page 13). This is inconsistent with the currently claimed background parameter, which is instead measured as non-specific binding *to the first and second test areas* (which have specific receptors coated thereon). For these reasons, the disclosed "background of the sample" fails to convey evidence of possession of the "test area-specific background" now claimed.

As to the "background of a negative control", page 11 of the specification describes the integration of control spots in the solid phase. This suggests that separate negative control areas, rather than the actual test areas themselves, are assessed in order to calculate the cut-off limit.

Furthermore, the specification does not provide details regarding the nature of the "control areas". As such, one skilled in the art would not envisage possession of methods in which non-specific binding *to the first and second test areas* was assessed in order to measure test area-specific background. The specification also does not disclose (for example) using one control area to correspond to each test area, such that the control areas would not be understood to be "test area-specific". The detailed elements now recited in the claim (background due to signal generating group non-specifically bound) cannot be envisaged from the general disclosure of "control areas".

Finally, it is not apparent that either of the disclosed background parameters ($background_{sample}$ or $background_{negative\ control}$) would be assessed on the first and second test areas *in the absence of analyte* as now required by the claims. Further, since the sample has already been contacted with the solid phase in step (b) "so as to allow binding of the plurality of analytes [in the sample] to the first and second test areas", the claim apparently suggests that the same test areas are being measured both in the presence and in the absence of analyte (see rejection under § 112, 2nd paragraph below). Such a scenario is not described in the specification.

For all of these reasons, neither explicit nor implicit support could be found for the claimed subject matter.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 44-48, 73, 75-77, and 81-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. Claim 44, step (d), recites:

> calculating a test area-specific cutoff on each test area based on a test area-specific background measured in the absence of the plurality of analytes, wherein the test area-specific background is detected from a signal generated by any signal generating group non-specifically bound to the at least first or second test area in the absence of any analyte of the plurality of analytes,
>
> wherein the signal generated in the presence of the plurality of analytes by the signal generating group bound to the first or second test area above the test area-specific cutoff is classified as a positive result, and wherein a positive result obtained from at least one of the first and second test areas is indicative of the presence of the pathogen in the sample.

This step invokes measuring background on the first and second test areas *in the absence of any analyte*. However, step (b) of the claim recites:

> contacting the sample with the solid phase…so as to allow binding of the plurality of analytes [in the sample] to the first and second test areas"

As written, the claim therefore appears to suggest that the same test areas are being measured both in the presence and in the absence of analyte. It is unclear how background measurements could be performed on the first and second test areas *in the absence of analyte*, as per step (d), when these same test areas have been previously contacted with analytes in the sample.

Perhaps Applicant intends that background measurements would be performed on test areas having the first and second analyte-specific receptors bound thereto, but that this is done as

part of a separate analysis--one analogous to that performed on the sample, but in the absence of analyte?

For the purposes of examination, the claims have been assumed to refer to test area-specific background measured in the absence of analyte and on test areas meeting the specifications of part (a), but in which the measurement may be performed in a separate or parallel analysis, such as on an additional solid phase having analogous first and second test areas with first and second analyte-specific receptors bound thereto. In other words, it is presumed that both analyte and background measurements are performed on multiple test areas having first and second analyte-specific receptors bound thereto, but that these measurements need not be performed on the *same* first and second test areas that have been contacted with the sample.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 44, 46-48, 73, 76-77, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karl et al. (WO 99/05525).

It is noted that while the Karl et al. reference is a German language document, an English language translation is available by way of its U.S. counterpart, US 6,815,217 B2. The column and line numbers indicated below refer to the text of US 6,815,217 B2.

Karl et al. teach a method for detecting at least one analyte in a sample using a solid phase having at least one spatially discrete test area. See the abstract and column 1, line 66 to column 2, line 61; column 6, lines 56-64; and claim 17 in particular. The solid phase is preferably non-porous, e.g. plastic, glass, metal, or metal oxide (column 2, lines 29-32). In one embodiment, both a protein of a pathogen (HBs antigen) and anti-HBc antibodies specific for the pathogen (hepatitis B virus) are assayed. This is done using immobilized antibody specific for HBs antigen (i.e., first receptor) and immobilized HBc antigen (i.e., second receptor), which are bound to discrete test areas on the solid support. See Figure 1 and column 2, lines 3-20, 34-39, and line 62 to column 3, line 14.

Karl et al. further teach contacting the sample with the solid support and with a detection reagent, namely a third receptor ("specific binding reagent") having a suitable marker group, e.g. fluorescent marker group. The detection reagent may be a "universal" marker group. See column 2, lines 39-64; column 3, line 17; claim 34, step (b) and Figure 1. The signals from the marker groups are detected and separately measured for each test area (see column 6, lines 34-45 and the Tables presented in the Examples). This is also made clear for example in claim 19, where test and control areas are separately measured in steps (c) and (d), respectively.

Karl et al. further teach calculating a cut-off, above which the test is considered positive. See column 5, line 66 to column 6, line 45, and in particular in the tables presented in the examples. This cut-off is "based on" the signal that was observed for a negative control sample binding to a signal test field (which contained anti-HBsAg antibody as receptor for HBsAg). See the equations for the Cut-off index presented in the legends for the Tables on columns 8-11, in particular the parameter "signal (negative control)". One of ordinary skill in the art would at once

envisage that the "negative control sample" of Karl et al. indicates a sample that does not contain the analyte to be determined. The resulting measurement may therefore be considered to represent background measured in the absence of the plurality of analytes. In addition, it is evident from Examples 2-4 that the determination of the signal from the negative control was performed in a test area-specific manner, since these examples involved multiple areas having different antibodies, and the signal due to the negative control is reported for each area.

The teachings of Karl et al. differ from the claimed invention in that the reference only illustrates calculating a cut-off in Examples which involved determination of a single analyte of a pathogen (HBsAg). Although the reference elsewhere teaches determination of both HBs antigen and anti-HBc antibodies on a single solid phase (Figure 1 and column 2, lines 66-68), Karl et al. do not exemplify calculating a cut-off for this embodiment.

Consequently, the reference fails to specifically teach a test area-specific background that is detected from non-specifically bound signal-generating group *bound to first and second test areas that have receptors specific for different analytes of the same pathogen*.

However, Karl et al. do clearly illustrate calculating the signal due to the negative control signal in each of multiple test areas. For example, in Example 2 the negative control signal is reported not only for the test area containing immobilized anti-HBsAg but also for three other test areas containing distinct antibodies (see Table bridging columns 8-9). Thus, these background measurements are clearly being assessed in a "test area-specific" manner.

Consequently, although Karl et al. do not specifically exemplify a test area-specific background for situations in which multiple antigens or antibodies of a given pathogen were assessed, it would have been obvious to measure test area-specific backgrounds in such contexts

in the same manner illustrated for other embodiments. In particular, in light of the teachings of Karl et al. regarding the advantages of performing multiple tests simultaneously on one sample (see especially columns 2 and 6), and the specific illustration of simultaneously assaying HBs antigen and anti-HBc antibodies, as well as the teachings that test area-specific background signals measured in the absence of analyte can be used to calculate test area-specific cut-offs that distinguish positive from negative tests, one of ordinary skill in the art could have combined these elements as claimed according to the disclosed methods in a predictable manner. One would be motivated to do this in order to correctly determine the presence of HBs antigen and/or antibodies, and therefore the presence of hepatitis B virus.

With respect to claim 46, Karl et al. teaches that the test areas occupy defined areas that are spatially separated from each other, and that miniaturized test areas with a diameter of 10 microns (0.01 mm) to 2 mm are most preferred (column 2, lines 9-10). Because the prior art range of 0.01 to 2 mm largely overlaps the claimed range of 0.01 mm to 1 mm, a *prima facie* case of obviousness also exists. See MPEP 2144.05. In particular, it would have been obvious to one of ordinary skill in the art to arrive at the claimed range during the course of routine optimization by choosing from values within the prior art range. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With respect to claim 47, Karl et al. teach control areas for detecting false results caused by interferences (see, e.g., the abstract; column 1, lines 11-33; column 2, lines 21-28; column 3, line 30 to column 4, line 60; and column 10, lines 45-49).

With respect to claim 48, Karl et al. teach universal marker groups comprising fluorescent latex beads (column 2, lines 62-67 and Figure 1).

With respect to claim 81, Karl et al. teach detection of the hepatitis B antigen HBsAg as well as of antibodies to the hepatitis B antigen HBcAg (Figure 1 and column 2, line 62 to column 3, line 14).

18. Claims 45 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karl et al. in view of Schonbrunner (GB 2 313 666 A).

Karl et al. is as discussed in detail above, which teaches a method substantially as claimed in which a sample is simultaneously analyzed to determine multiple analytes on a single solid phase. The reference exemplifies determining HIV antibodies, HBs antigen and HBc antibodies (see Figure 1). Karl et al. therefore teaches HIV antibodies as possible analytes but does not specifically teach determining a plurality of HIV antigens in addition, nor does the reference specify the particular HIV antigens or antibodies recited in claim 75.

Schonbrunner et al. teaches simultaneous detection of the presence of both antigen and antibody analytes of HIV in a sample. As with the methods of Karl et al., Schonbrunner et al. also teaches that either antigens or antibodies can be attached to solid supports in order to detect HIV antibody and antigen, respectively (page 20). Schonbrunner et al. further teaches that detection of the presence of both antigens and antibody analytes of HIV closes the diagnostic window, providing the possibility for specifically detecting the presence of HIV in a sample at a very early stage of infection. See page 1, first paragraph; pages 2-3; and pages 5-7, especially at the paragraph bridging pages 2-3 and at page 6, lines 26-29.

Schonbrunner et al. contemplates the particular HIV-1 antigen p24, as well as other HIV-1 gag antigens (page 6, lines 29-32 and page 25). The reference also teaches detection of antibodies to HIV gp41 (page 26, lines 4-9).

Therefore, it would have been further obvious to one of ordinary skill in the art to employ the methods of Karl et al. in order to detect both HIV antigen(s) (e.g., p24 or gp41) in addition to the anti-HIV antibodies taught by Karl et al. because this would allow for HIV to be detected at an earlier stage of infection, thereby closing the diagnostic window. It would have been further obvious to select those anti-HIV antibodies that target HIV gp41, as taught by Schonbrunner, by selecting from a finite number of identified, predictable solutions; namely identified HIV antigens known to be capable of eliciting an antibody response.

19. Claims 44-45, 47-48, 73, 75-77, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor (US 5,627,026) in view of Osther et al. (U.S. 5,008,813) and either one of Bayer et al. (CA 2109239) or Tidey et al. (U.S. 6,046,013).

O'Connor et al. teach a method of detecting a plurality of analytes, namely both an antibody to and an antigen of an infective agent, in a single sample aliquot. See the title, abstract; and column 1, line 58 to column 4, line 41. The infective agent may be FeLV, FIV, or HIV (column 4, lines 14-30) and simultaneous assessment of antigens and antibodies associated with the same viral infection (i.e. a pathogen) is clearly disclosed (column 4, lines 23-25).

The method of O'Connor et al. involves (a) providing a solid phase (solid support), which may be a non-porous material such as a microtiter well, or a glass, plastic, or latex bead (see especially column 3, lines 17-29; column 4, line 65; column 6, line 57 to column 8, line 3). An

antigen capable of selectively forming an immune complex with a sample antibody (i.e., first analyte-specific receptor) is bound to the solid support at a first location, while an antibody capable of selectively forming an immune complex with a sample antigen (i.e., second analyte-specific receptor) is bound to the solid support at a separate position (see column 2, line 4 to column 3, line 7; and especially claims 1, 7, 9, and 14).

O'Connor et al. further teaches (b) contacting the sample with the solid phase and with detectable reagents. See column 3, lines 8-51, and claim 1 in particular. For example, O'Connor et al. discloses the use of a labeled antigen (i.e., third receptor) that selectively binds to a captured antibody from the sample, together with the use of a labeled antibody (i.e., another third receptor) that selectively binds to a captured antigen in the sample in a method for detecting both antibody and antigen in a single sample (claim 1). The signals generated by the detectable labels are (c) separately measured or assessed (column 5, lines 43-47 and line 65 to column 6, line 6; and the claims, e.g. claim 1, step (e)).

Regarding the step of calculating a test area-specific cut-off, O'Connor et al. exemplifies an ELISA test for FIV antibody in which non-FIV reactive feline serum was used as a negative control (see column 8, line 29 to column 9, line 25. Wells coated with FIV antigen (i.e., analyte-specific receptor) were incubated with the sample to be tested so as to allow antibody in the sample to bind to the FIV antigen (see especially column 8, lines 45-58). In the same manner, an antigen-coated well was also incubated with negative control serum. See column 8, lines 59-60. The signal (absorbance at 650 nm) due to this negative control was measured; any bound label measured in this case would be attributable to nonspecific binding since no analyte was present (i.e., the background signal in the absence of analyte). The presence of antibody to FIV is

determined by relating the signal of the sample to the negative control signal. In particular, O'Connor et al. selected a cutoff of 3 times the absorbance signal due to the negative control sample, so that anything above this cutoff was regarded as a positive sample (see column 9, lines 20-25).

It is clear from the teachings of O'Connor et al. that each well is separately assessed for signal. Furthermore, the reference makes clear that the absorbance intensity of each well was compared to the negative control. Likewise, in the embodiments involving a filter as the solid support, the reference makes clear that each *respective* sample spot is assessed in relation to a control spot in order to determine whether the assay results are positive (see column 5, line 48 to column 6, line 6). Consequently, this comparison of sample signal to negative control signal would be considered a "test area-specific" cutoff.

The O'Connor et al. reference differs from the claimed invention in that the use of a negative control sample (i.e., background measured in the absence of analyte) is only discussed in the context of the FIV antibody ELISA test, which involved only this single analyte and not a plurality of analytes. Although the reference elsewhere teaches detection of a plurality of analytes, cutoff levels based on the use of negative control samples are not explicitly disclosed except in the case of the FIV antibody example. In other words, O'Connor et al. measures background in the absence of analyte on a test area having an analyte-specific receptor bound thereto, but only exemplifies this type of background measurement for an assay that determined a single analyte rather than a plurality of analytes.

O'Connor et al. therefore fails to specifically illustrate measuring a "test area-specific" background measured on the *first or second test area*, since in the FIV antibody ELISA test exemplified there was only one type of test area.

At issue, therefore, is whether it would be obvious to also perform such background measurements in the same manner on each type of test area (i.e., in a "test area-specific" manner) when using multiple types of test areas to simultaneously assay both antigen and antibody according to the other disclosed embodiments of O'Connor et al.

Osther et al. also relates to assays for detecting the presence of antibodies, and teaches that a negative control provides information about the absence of reactive antibodies in a sample that are specific to the particular analyte-specific receptor ("test antigen") that is being used for the assay (see column 1, lines 19-61, especially at lines 47-61). A negative control also provides information as to the reaction level at which a specimen may be considered reactive: the cut-off point in a particular test is often based on the relative value obtained by a positive and/or negative control (ibid). The negative control value thus affects the specificity of the test system.

The teachings of Osther et al. therefore indicate that those of ordinary skill in the art recognized the value of negative controls in providing information about the particular analyte-specific receptor being used in assays to detect analytes (in this case, antibodies); as well as in establishing a cut-off point.

Furthermore, it was known in the art when conducting measurements for a plurality of analytes using a plurality of analyte-specific receptors to measure the background signal due to a negative control sample for each different receptor, i.e. a test area-specific background.

For example, Bayer et al. teach methods for simultaneous determination of antigens and antibodies using multiple receptors immobilized on a solid phase (abstract and page 1). In Example 1, Bayer et al. determined both HIV antigens and anti-HIV antibodies using multiple HIV antigens and antibodies as analyte-specific receptors (pages 14-17). Measurements were obtained for each different type of receptor for both serum samples and for a negative control sample (Table 1).

Tidey et al. teaches testing patient samples for a plurality of antibodies against different HLA molecules, by testing serum samples for reactivity with forty wells (test areas) containing a specific HLA molecule (abstract; column 2, line 38 to column 3, line 21; and columns 5-7). In addition to test samples, a known negative sample is also measured in the same way for each test. In this way, different background levels are obtained for each antigen, which are subsequently used to determine cutoff values above which an assay is defined as being positive (columns 5-7).

The teachings of Bayer et al. and Tidey et al. therefore indicate that it was known to measure the background due to a negative control for each different type of receptor used in assays for detecting a plurality of analytes, i.e. to measure "test area-specific" background.

Consequently, when simultaneously assaying both antigen and antibody according to the methods of O'Connor et al., it would have been obvious to one of ordinary skill in the art to measure the background signal due to the negative control sample for each type of test area (i.e., each different immobilized antigen/receptor on the solid phase) in a test area-specific manner because such negative control measurements were of recognized value in providing information about a particular test reagent for detecting an analyte. For example, it would have been obvious to select a cutoff of 3 times the absorbance signal due to the negative control sample (as taught by O'Connor et al.) for each respective test area and to designate test areas with a signal greater than cutoff as positive. Such a cutoff would be said to be a test area-specific cutoff based on a test area-specific background as claimed.

Motivation to combine the reference teachings in this manner comes from the teachings of Osther et al., which indicate that those of ordinary skill in the art recognized the value of negative controls in providing information about the particular test reagent used to detect the analyte of interest.

As such, when using multiple receptors to detect multiple analytes, one would be motivated to perform a negative control on each different receptor and use such test area-specific background measurements as the basis for determining whether each test area was positive or negative.

Furthermore, because this known technique of assessing a negative control on each of multiple test areas (i.e., test area-specific background in the absence of analyte) was taught in the prior art (by both Tidey et al. and Bayer et al.), one of ordinary skill in the art would have

recognized that applying this known technique would have yielded predictable results and resulted in an improved method. In particular, given the recognized value and widespread use of negative controls, it would have been a matter of routine skill in the art to construct negative controls for both antigen and antibody analytes to be detected by combining the prior art elements.

Put another way, given that O'Connor et al. focus on the simultaneous determination of both antibody and antigen in a sample, it would have been obvious to one of ordinary skill to perform negative control background measurements for each immobilized receptor in the same manner exemplified for FIV antigen when using a plurality of receptors to detect both antigen and antibody analytes. Similarly, it would have been obvious to relate the signal value of the sample to the signal value of the negative control for each receptor/ test area used. For example, when detecting FIV antigen in addition to FIV antibody, it would have been obvious to include a negative control for FIV antigen and to relate the signal from an FIV antibody-coated well to the signal from the negative control, thereby measuring background due to non-specific binding.

Furthermore, it would have been obvious to apply the known technique for analyzing the results from each reaction (e.g., from each sample well) in the same manner as described for the FIV antibody. One would be motivated in light of the clear teaching of O'Connor et al. that this relation of sample signal to control signal allows for the validity of the assay to be determined. As such, it would have been obvious to calculate a cutoff of three times the negative control absorbance for antibody as well as for antigen in order to determine whether the sample was in fact positive for the presence of each of these analytes.

With respect to claim 45, O'Connor et al. teach detection of both HIV antigen and anti-HIV antibody (column 4, lines 23-25). Hepatitis B (i.e., HBV) antigen is also contemplated (see column 4, lines 6 and 17 and claim 13).

With respect to claim 47, O'Connor et al. teach controls, e.g. control wells coated with receptor and to which positive or negative control sample is added (column 3, lines 26-29; column 5, line 48 to column 6, line 6; and column 8, lines 59-65). A negative control can be performed by coating spots with a non-specific antibody (column 5, lines 48-65). This is done to control for nonspecific reactions, i.e. "interferences".

With respect to claim 48, O'Connor et al. teaches detection reagents comprising a third receptor specific for the analyte (e.g., antibody or antigen specific for antigen or antibody, respectively) bound directly to a signal-generating group (enzyme). See column 3, lines 8-51; column 7, lines 8-30 and 47-51; column 8, lines 50-56).

With respect to claims 73 and 75, O'Connor et al. teaches detecting HIV p24 antigen and anti-HIV antibody (column 4, lines 23-30).

With respect to claim 76, O'Connor et al. teaches that the detectable labels may be enzyme labels (column 3, lines 47-51).

With respect to claims 77 and 81, O'Connor et al. teaches detection of Hepatitis B (i.e., HBV) antigen (see column 4, line 6) but fails to specifically teach detection of more than one analyte "derived from" HBV. Nonetheless, O'Connor et al. teach simultaneous assaying for antigens and antibodies associated with the same viral infection (column 4, lines 23-25). Although HIV and not HBV is exemplified in this context, it would have been obvious to one of

ordinary skill in the art to select HBV from the finite number of viruses disclosed in the reference and to detect both HBV antigen in addition to anti-HBV antibody. One would be motivated to do this in order to assay for the presence of HBV virus.

20. Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor et al. in view of Osther et al. and either one of Bayer et al. or Tidey et al. as applied to claim 44 above, and further in view of Ekins (US 5,837,551).

O'Connor et al. is as discussed above, which teaches test areas on non-porous solid supports such as microtiter plates. However, the reference fails to specifically teach that the test areas have diameters of 0.01 – 1 mm.

Ekins teaches forming arrays of "microspots" in which binding agents (i.e., receptors) are immobilized into defined, spatially separated test zones (i.e., "test areas") on a solid support (column 2, line 35 to column 4 line 41). The microspots preferably have an area of less than 1000 square microns, e.g. 0.1 square mm, and can be for example of diameter 80 microns or 0.08 mm (column 3, lines 34-63; column 4, line 2). By providing such microspot arrays, a plurality of analytes may be simultaneously determined (column 3, lines 40-47). The microspots can be formed on a microtiter plate, i.e. non-porous support (column 7, lines 33-40). Binding of analytes to the binding agents immobilized in each microspot is then assessed using a detection agent capable of binding to the analyte and including a marker, e.g. an enzyme or fluorescent marker (column 3, lines 10-33).

Such miniaturized test zones contain small amounts of binding agent, allowing binding assays to be conducted with rapid kinetics to minimize the time needed to complete the assay

(column 6, lines 4-8). In addition, less of the binding agent is necessary, diffusional constraints are reduced and assay sensitivity is also improved (column 6, lines 9-32).

Therefore, it would have been obvious to one of ordinary skill in the art to modify the method of O'Connor et al., Osther et al., and Bayer et al. (or alternatively O'Connor et al., Osther et al., and Tidey et al.) by depositing the first and second receptors into small test zones or "microspots" (e.g., of diameter 0.08 mm on a microtiter plate) as taught by Ekins et al. because detection of antibody and antigen could be conducted more rapidly and with greater sensitivity and would also require less of the capture reagents to be consumed.

When performing the prior art methods using microspots in this manner, it would have been further obvious to employ the detection scheme taught by Ekins to be suitable for the microspot arrays, namely by using a detection agent capable of binding to analyte (i.e., third receptor) and including a marker capable of producing the signal for the assay.

21. Claim 82 is rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor in view of Osther et al. and either one of Bayer et al. or Tidey et al. as applied to claim 44 above, and further in view of Miyamura et al. (U.S. 5,714,314); or, in the alternative, as being unpatentable over Karl et al. in view of O'Connor et al. and Miyamura et al.

O'Connor et al. and Karl et al. are as discussed in detail above. O'Connor et al. teaches simultaneous assay for antigens and antibodies associated with the same viral infection, e.g. HIV antigen and anti-HIV antibody, in order to rapidly screen blood or other biological fluids for infective agents such as HIV (see column 4, lines 14-30). The reference also mentions hepatitis in general, teaching how hepatitis antigen and anti-hepatitis antibody can be immobilized onto

the solid support (to thereby detect hepatitis antibody and antigen, respectively). See column 2, lines 40-59 and column 3, lines 17-29). However, the reference fails to specifically teach detection of hepatitis C virus antigens or antibodies.

Karl et al. teaches assaying for HBV antibodies and antigens using immobilized HBs antigen and anti-HBs antibody, respectively (see especially Figure 1). However, the reference fails to specifically teach assaying for antibodies or antigens of HCV.

Miyamura et al. teaches that HCV was known in the art to be one type of pathogenic virus causing viral hepatitis. The reference further teaches that HCV was known as a grave infectious disease worldwide, and the prevention, early diagnosis, and treatment thereof were of recognized importance. See column 1, lines 30-44. Miyamura et al. also discuss how hepatitis C antigen can be used to detect antibody to HCV, e.g. in blood samples (abstract).

Therefore, it would have been obvious to one of ordinary skill in the art to select HCV (as taught by Miyamura et al.) as the type of viral infection to be screened in the method for simultaneous assay for antigens and antibodies associated with the same viral infection of O'Connor et al. More particularly, it would have been obvious to employ anti-HCV antibody and HCV antigen as first and second receptors to detect HCV antigen and anti-HCV antibody, respectively, as the plurality of analytes. One would be motivated to do this because HCV was recognized as a disease of significant clinical concern, as taught by Miyamura et al. Motivation to combine the references also comes from the teachings of O'Connor et al., who teach detection of hepatitis in general albeit not the subtype of HCV.

Similarly, although Karl et al. exemplify detection of HBV antibodies and antigens, it would have been obvious to one of ordinary skill in the art to detect HCV antigens and

antibodies in light of the teachings of Miyamura et al. that HCV was of significant clinical concern. When taken together with the teachings of O'Connor et al. that simultaneous assays that screen for both antigens and antibodies in a single test provides a means for rapid screening for infective agents, one would be motivated to detect HCV antibodies and antigens simultaneously a single test in order to rapidly screen for the presence of HCV.

One would have had a reasonable expectation of success because anti-HCV antibodies and HCV antigens were known in the art, as taught by Miyamura et al.

Response to Arguments

22. Applicant's arguments filed 7/6/2009 have been fully considered.

23. With respect to the rejections under § 112, 1st and 2nd paragraphs, Applicant's arguments have been considered (Reply, pages 6-7) but are moot in view of the new ground(s) of rejection.

24. With respect to the rejections under § 103(a) based upon the Karl et al. reference, Applicant argues that Karl et al. is disqualified as prior art because the instant application is entitled to earlier foreign priority dates. This is not found persuasive Applicant is not considered to be entitled to the earlier dates for the reasons noted above (see ***Priority***).

25. With respect to the rejections under § 103(a) based upon the O'Connor et al. reference as set forth in the previous Office action, Applicant's arguments have been considered (Reply, pages 9-13) but are moot in view of the new ground(s) of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Christine Foster/
Examiner, Art Unit 1641